

Autoimmune disease and the Immune system—general principles

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Immunology...

- Simple definition: The study of the physiologic mechanisms that allow the body to recognize pathogens and foreign proteins *as self vs. non-self* and to **neutralize** or **eliminate** those unfamiliar pathogens and proteins.
- FOUR General Principles...

General principle #1—the ability to recognize of SELF vs. Non-SELF

- The 2 classes of self-antigens that make each of us unique are referred to as HLA antigens
- Class I antigens—found on all body cells (except RBCs); HLA-A, HLA-B, HLA-C—known as Class I antigens
- Class II antigens— known as HLA-DP, HLA-DQ, HLA-DR

Class II HLA antigens

- The Class II antigens determine which foreign antigens an individual responds to as well as the strength and type of response and are essential for immune function and survival
- These are also “secreted” in body fluids in “lower” forms of animals— help select a mate based on “strength” of the immune system to guarantee survival of the species—how do lower forms of animals meet? Dogs stick their nose where the “sun don’t shine” and say... “*You’re the one for me...*”
- Known as clonal selectivity

Because we have a “mother”—your frontal lobe...

- “*Don’t even think about it...*”
- CN 0 (zero) –The nervus terminalis—runs in parallel with cranial nerve 1 (the olfactory nerve) human pheromones—pheromones...saliva? Sniff? Kiss?

Just remember, ladies (or gentlemen)...you’ve got to kiss alot of toads before you find your prince or princess

- And it all has to do with those pheromones...

Autoimmune diseases and HLA (self antigens)

- Autoimmune diseases and specific HLA-antigens—an individual will inherit specific HLA-antigens that “predispose” that individual to an autoimmune disease
- Some of these include:
 - Rheumatoid Arthritis (HLA-DR1, DR4)
 - Multiple sclerosis (HLA-A8, B8, DR3—10x greater risk)
 - Celiac Disease (HLA-DQ2, DQ8)
 - Type 1 Diabetes—HLA-DR3, DR4, DQB1

Type 1 diabetes—

- As mentioned...Type 1A diabetes—HLA-DR3 (5% risk), HLA-DR4 (6% risk), both? (20% risk), and DQB1—more prevalent in Scandinavians (Finland)
- Blonde-hair, blue-eyed kid named....

Named Sven—drinkin’ and peein’ too much...

Polyuria (excessive urination), polydipsia (excessive drinking), polyphagia (excessive eating), weight loss, fatigue

Historical highlights

- Over a 100 years ago bacteriologist Paul Ehrlich coined the term “horror autotoxicus”—a term used to describe an immune system attack against a person’s own tissues.
- He thought such “autoimmunity”—another term he coined—was biologically possible yet somehow kept in check, but he wasn’t sure how—it really didn’t matter, no one believed him...fast forward—

There are over 80 autoimmune disorders today, involving approximately 50 million Americans...

- Rheumatic—rheumatoid arthritis, psoriatic arthritis
- Neurologic—multiple sclerosis, myasthenia gravis, PANS (Pediatric Acute-onset Neuropsychiatric Syndromes)
- Vascular—Kawasaki disease in kids, Henoch-Schönlein purpura in kids, ITP in kids (immune thrombocytopenic purpura) or adults
- Endocrine—Hashimoto’s thyroiditis, Grave’s disease, Addison’s disease
- Dermatologic—dermatomyositis, alopecia areata, psoriasis

Over 80 autoimmune diseases affecting ~50 million Americans

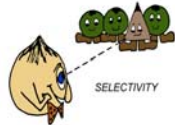
- Gynecologic—endometriosis
- GI—Crohn’s disease, ulcerative colitis, celiac disease
- Hematologic—AIHA (autoimmune hemolytic anemia), pernicious anemia
- Multi-system—systemic lupus erythematosus, MCTD (mixed connective tissue disease also known as “overlap” syndrome—features of 2 or more autoimmune diseases), polymyositis, systemic sclerosis (scleroderma)

Where there's smoke, there's fire...

- Familial clustering of autoimmune diseases (Mom with "lupus" (SLE), daughter with MS, sister with Hashimoto's thyroiditis)
- Individuals with a cluster of autoimmune diseases--Hashimoto's Thyroiditis + Type 1 DM + celiac disease triad
- Rheumatoid Arthritis + Sjögren's—30-50% of patients with RA have Sjögren's (autoimmune attack on secretory glands—dry eyes, dry mouth, dry "everything")
- 8-30% of Systemic Lupus Erythematosus patients have systemic sclerosis
- Endometriosis —7x more likely to have Hashimoto's; higher risk for MS, RA, lupus, Systemic Sclerosis (*Human Reproduction* 2002)

2nd general principle—selectivity and specificity

- The immune system is highly selective and specific for each pathogen
- 1 pathogen=1 response
- **"monoclonal"**



For example...streptococcus

- How many types of strep are there?
- Over 200 types (Group A thru O + hemolytic properties—alpha, beta, gamma)—Just because you have had 1 strep throat doesn't mean you're "immune" to all strep infections--BUMMER
- GABHS (Group A beta hemolytic strep)— is the worst of the bunch and causes the most problems
- One type of pathogen = one response to that pathogen

**“Mono” clonal also applies to a class of drugs—
monoclonal antibodies (last name MAB)**

- Monoclonal antibodies have been produced for a myriad of disease processes: specific types of cancer; **for specific targets in the immune system responsible for various autoimmune diseases**; to reduce allergic symptoms;
- Two of the most successful monoclonal antibodies produced thus far are used for autoimmune diseases. These two antibodies target the overproduction of Tumor Necrosis Factor alpha (TNF-a), the inflammatory protein overproduced in Crohn’s disease, Ulcerative Colitis, rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.
- Infliximab (Remicade) (1999)
- Adalimumab (Humira) (2002)

3rd general principle—memory

- Once having met a pathogen, the immune system “never” forgets it.
- If you are re-challenged with the same pathogen the memory response (the anamnestic response) will recognize it immediately-- and destroy it or neutralize it.

**How does the immune system develop
memory?**

- B lymphocytes/plasma cells produce antibodies (humoral immunity) to specific antigens/pathogens, measured as antibody “titers”—ASO titers, EBV titers, varicella titers, CMV titers
- When “self” antigens become foreign, antibodies are made to various components—hence the term autoantibodies

Auto-antibodies in autoimmune diseases

- Anti-mitochondrial antibodies—autoimmune primary biliary cirrhosis (95%) of patients
- Rheumatoid factor—(70-80%); anti-citrullinated antibodies for Rheumatoid arthritis
- Anti-transglutaminase antibodies in celiac disease
- Anti-thyroglobulin, anti-TPO—Hashimoto's thyroiditis
- Anti-islet cell and anti-GAD antibodies (Type 1 Diabetes)
- Anti-nuclear antibodies (ANA)—normal titer is 1:2 - 1:40 (found in 5% of healthy adults); if the diagnosis of lupus is considered and the ANA's are negative, it is NOT lupus; negative predictive value is 99%
- The higher the titer the more specific
- In general, the lower titers (below 1:40) are less specific

In addition to autoantibodies, what else can antibody titers tell us?

- 1) tell us if you have EVER been exposed to a specific pathogen via disease or immunization, ie. memory—varicella titers, CMV titers, measles titers, HBV titers
- 2) tell us if you have responded to a pathogen/**vaccine** and how strong that response was/or currently is—levels of titers
- 3) antibodies can tell you something about the disease stage (IgM vs. IgG—acute phase (IgM) vs. convalescent phase (IgG))

Memory of the cell-mediated system (T lymphocytes) can be measured as well—TST

- The tuberculin skin test (TST), which dates back over 100 years-- evaluates cell-mediated immunity and consists of the intradermal injection of a small amount of purified protein derivative from the *M. tuberculosis* bacteria.

Antibody titers that we developed as kids wane with aging...

- We just can't remember like we used to...☺
- Neither can our immune system

Memory and “resistant-to-kill” pathogens

- The immune system can recognize and remember, but not kill certain pathogens
- The Herpes family of viruses (100%)
- Hepatitis C virus cleared in 15-20%, chronic in 75-80%,
- HBV cleared in 95% of adults; chronic HBV in 5% of adults. Approximately 90% of infected infants will develop chronic infection. The risk goes down as a child gets older. Approximately 25%–50% of children infected between the ages of 1 and 5 years will develop chronic hepatitis B;
- tubercle bacillus (TB)

Memory and the “family” of herpes viruses

- the herpes viruses...the immunocompetent immune system keeps herpes virus's in check; when immunocompromised? Herpes viruses re-express themselves
- Implications for patients with autoimmune disease or on immunosuppressive drugs? HSV-1, HSV-2, and VZV live in the the nervous system and remain dormant for as long as the immune system is healthy
- Autoimmune diseases and immunosuppressive drugs increase the risk for the herpes viruses to “express” themselves...
- high-dose prednisone
- TNF-alpha antagonists (adalimumab/Humira, infliximab/Remicade),
- janus kinase inhibitor (tofacitinib/Xeljanz)
- etanercept/Enbrel

Immunocompromised patients? Shingles is common

- Lupus patients—risk of shingles is between 3.2-21%
- Patients with hematologic malignancies (leukemia, lymphoma, multiple myeloma) have a 3x higher risk of herpes zoster
- Age increases the risk as the immune system declines in function
- HZO (herpes zoster ophthalmica is the fastest rising area presenting with shingles)

The NEW, and very much IMPROVED, “Shingles” vaccine--SHINGRIX

- A single-protein recombinant subunit vaccine has been shown to be ~97% effective
- The vaccine contains varicella zoster virus (non-live) with a subunit antigen system to boost immunity
- Zostavax is HISTORY...

The scoop on Shingrix

- 97% effective vs. the old Zostavax @ 51%
- Immunity lasts longer than Zostavax
- 2 IM doses (separated by 2-6 months) vs. 1 SQ dose of Zostavax
- Should get Shingrix even if you have had Zostavax—wait at least 8 weeks after Zostavax
- Shingrix can be given to immunocompromised patients

4th general principle—inflammation and immunity go “hand-in-hand”

- The inflammatory response is an integral part of the immune response—it’s innate vs. the “learned” response of the immune system
- Inflammation helps to destroy “foreign antigens” and/or pathogens
- The immune system can easily trigger the inflammatory response
- Lot’s of “itis’s” in autoimmune disease—autoimmune glomerulonephritis, autoimmune hepatitis, lupus nephritis, ulcerative colitis, Hashimoto’s thyroiditis

The “spectrum” of autoimmune disease

- Autoimmune disorders form a spectrum— on end of the spectrum are conditions in which “autoantibodies” (antibodies against proteins on ‘self’ tissues) are directed against a single organ, tissue, or protein, therefore resulting in local tissue damage (but can obviously have a wide range of effects)—examples: Hashimoto’s thyroiditis (thyroglobulin, thyroperoxidase), Myasthenia Gravis (nicotinic acetylcholine receptors at the NM junction), Multiple Sclerosis (“many scars”)(myelin basic protein)
- On the other end the autoimmune disease can damage multiple tissues—in other words, it is more “systemic” (systemic lupus erythematosus, rheumatoid arthritis)

Single organ—the thyroid gland: Hashimoto’s thyroiditis

- Anti-thyroglobulin antibodies; anti-thyroperoxidase antibodies (TPO)
- Trigger inflammation and destroy the ability of the thyroid gland to produce adequate amounts of T₃ and T₄
- Results in a debilitating range of systemic effects as thyroid hormone is necessary for metabolism in ALL tissues...

Hashimoto's thyroiditis (autoimmune) is the most common cause of hypothyroidism

- No energy, fatigue
- Can't remember; can't find a word; depression, dull personality
- Low heart rate (less than 60), respiratory rate 12 or lower; low temperature--hypothermia)
- weight gain (up to 15 pounds), fluid retention
- Dry hair, loss of hair (not noticed until greater than 50% is lost)
- Constipation—the "backdoor" diagnosis to hypothyroidism
- Problems with fertility; heavy periods, low libido
- Hypercholesterolemia (can't clear it out of the blood—70% have hypercholesterolemia)—1 in 7 people with high cholesterol has underlying hypothyroidism

The most common presentation of hypothyroidism in geriatrics

- Cognitive dysfunction may be the ONLY manifestation of hypothyroidism in the older patient...
- ALWAYS check thyroid function in any patient with cognitive dysfunction

Grave's disease—instead of too little...too much thyroid hormone...

- Weight loss despite normal/increased appetite
- Fatigue, exhaustion, insomnia
- Sinus tachycardia, palpitations, **atrial fibrillation**
- Tremor, hyperreflexia
- Muscle weakness
- Sweating, heat intolerance
- Exophthalmos, proptosis-- 25 and 50 percent of people with Graves disease have Graves ophthalmopathy.
- Most hyperthyroidism causes diarrhea

However...in the geriatric patient...

- Instead of diarrhea or more frequent bowel movements (which you would expect due to the increased metabolism), **more commonly there is a resolution of pre-existing constipation in the geriatric patient**
- A HALLELUJAH moment to be sure!! But be highly suspect of hyperthyroidism...**especially if the patient also has atrial fibrillation**

Multiple sclerosis—CNS demyelination; usually presents with a clinically isolated symptom + overwhelming fatigue

- Optic nerve demyelination as the first manifestation in many individuals— sudden loss of vision with optic neuritis
- Corticospinal tract demyelination—spasticity, hypertonia and hemiparesis/paralysis
- Cerebellar demyelination—balance and equilibrium problems; “puppet-like” movements; pendular reflexes; hypotonia
- Spinothalamic tract demyelination—pain (Lhermitte sign)—shock-like pain in neck; paresthesias
- Neurologic signs separated in “space” and “time”

On the other end of the autoimmune spectrum--systemic lupus erythematosus, SLE or “lupus”

- “LUPUS ERYTHEMATOSUS”—red wolf; butterfly rash
- Auto-antibodies directed DNA components (ANA), platelets (causing thrombocytopenia), RBCs (anemia)
- Antigen-antibody complexes (aka immune complexes) are formed and land in the microvasculature throughout the body triggering inflammation
- Affects many systems—skin (rash—70%), musculoskeletal (myositis—40%), renal (nephritis), cardiovascular (pericarditis), pulmonary (pleuritis), joints (arthritis)
- neuropsychiatric (personality changes, seizures, psychosis)

Autoimmune disease—female gender bias

- > 75% are women; peak incidence in 4th and 5th decade (30s-40s)—when the ovaries are in “full force”—estrogen is peaking...
- SLE, “lupus” -- (F10:1M)
- Rheumatoid arthritis -- (F7:1M)
- Sjögren’s -- (10:1)
- Hashimoto’s thyroiditis (studies vary widely from 8:1 to 25:1 to 50:1)
- Grave’s disease – (7:1)
- Multiple Sclerosis— (3:1)

Autoimmune diseases are tough to diagnose

- Takes an average of five visits to a healthcare professional over an average of 3.5 years to finally be diagnosed properly (American Autoimmune Related Diseases Association, March 2016)
- WHY? Lots of reasons. The symptoms vary widely and can overlap with other more benign illnesses
- One symptom that is uniform throughout most autoimmune diseases— **profound fatigue**; described as “debilitating” fatigue, “impacts every aspect” of their lives

HAVE A HIGH INDEX OF SUSPICION!!!

- Age – late 20’s – 40’s (there are always “outliers”)
- Gender – 75% female overall
- Family history – who’s your momma?
- Autoimmune diseases – “clustering”

Autoimmune diseases—it's more than just genetics

- You can have the genes that predispose to various autoimmune diseases, but environmental (exogenous) or endogenous triggers play a role in “turning on” the genes

How do endogenous and exogenous proteins trigger an immune reaction to “self”?

- The principle of molecular mimicry
- The “foreign” antigen (bacteria, virus) appears similar to an antigen on endogenous/normal tissue
- The immune response recognizes and attacks the foreign antigen, but “cross reacts” with the “self-antigen” due to similarities in the antigens between “self” and “non-self”
- Three examples come to mind immediately
- 1) Crohn’s disease and norovirus or perhaps an endogenous bacteria (microbiome)
- 2) Group A beta hemolytic strep (GABHS) and rheumatic heart disease
- 3) *Campylobacter jejuni*, Zika virus, and Guillain-Barre syndrome

Theories on why autoimmune diseases are “on the rise” today

- Lack of dirt
- Lack of vitamin D
- C-sections vs. vaginal delivery—the microbiome
- Bottle vs. breast milk—the microbiome

KIDS are too clean!

- Two pathways to take:
 - TH1 vs. TH2 pathway... Th1 pathway is the healthy pathway,
 - TH2 pathway increases risk for allergies and autoimmune disease (Type 1 diabetes, for example)
 - Pathogens in dirt help to prime the immune system and trigger the TH1 pathway—the healthy pathway
- Germphobic (mysophobic*) moms
(*irrational fear of DIRT)
- LET THEM EAT DIRT! **As early as possible!!!**
 - Okada H, Kuhn C, Feillet H, et al. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010;160(1):1–9.

Not enough sunlight, vitamin D deficiencies

- Sun-phobic and sunscreen maniac moms
- The overuse and abuse of sunscreen!! Slow down with the sunscreen use! SPF 15 reduces vitamin D absorption by 97.5%
- Kids playing videogames inside (the "thumb tribe")—get 'em outside
- Vitamin D deficiency pushes the immune system in the wrong direction—abnormal regulatory T cells?
- 2 pathways—TH1 and TH2
- Taking the TH2 pathway increases the risk of allergies and autoimmune disease

Decreased breast feeding

- Breast "microbiome"
- 30 percent of the beneficial bacteria in a baby's intestinal tract come directly from breast milk, and an additional 10 percent comes from skin on the mother's breast.
- The GOOD NEWS? Breastfeeding rates are rising in the United States. OVERALL U.S. numbers? 79% of newborn infants start to breastfeed. THE BAD NEWS? breastfeeding did not continue for as long as recommended. Of infants born in 2011, 49% were breastfeeding at 6 months and 27% at 12 months.

More C-sections vs. vaginal deliveries

- Vaginal microbiome
- "vaginal seeding"
- rate of cesarean delivery (CD) has risen 48% since 1996, reaching a level of 31.8% in 2007
- Concurrent with the trend of increasing CD, there has been an epidemic of both autoimmune diseases such as type 1 diabetes, Crohn's disease, and multiple sclerosis and allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis
- Okada H, Kuhn C, Feillet H, et al. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010;160(1):1–9.

INNATE IMMUNE RESPONSE...Barrier defense mechanisms and acute inflammation

- Skin, mucous membranes, saliva
- pH of body fluids
- How do we, as HCPs, disrupt the immune system in patients?
We break the barriers...change the pH (Drugs that change the pH of the stomach increase the risk for infection...PPIs)
- Gotta hole? We'll put a tube in it...if you don't have a hole for the tube we're holding—we'll make a new hole! Urinary catheters, Hickman catheters, ports, arterial lines, venous lines, surgical sites, J tubes, G tubes, IV tubes, trach tubes—pick a tube, any tube...

Innate defense: acute inflammation

- Vasodilation
- Increased permeability of vascular membranes
- Arrival of WBCs— the neutrophils as the first line of defense and then the macrophages

- RED, HOT, SWOLLEN, and PAINFUL

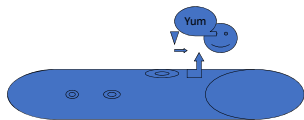
Acute inflammation—white blood cells

- Segs, aka neutrophils-- are the cells of acute inflammation—
- Segs respond directly to tissue damage, invasion by foreign pathogens and, to a signal from the specific immune response to attack tissues that the immune system has "marked" as foreign—NON-SELF
- Unfortunately, in autoimmune disease, the neutrophils play a major role in destruction of tissues such as the joints in patients with rheumatoid arthritis; in the kidneys in patients with lupus; in the white matter of patients with multiple sclerosis, severe inflammation in ulcerative colitis

CLINICAL CORRELATION:

- Neutrophils migrate into the large bowel in ulcerative colitis and contribute to the massive inflammation
- Vedolizumab— (Entyvio) blocks a protein called alpha-4-beta-7, an integrin, (an adhesion molecule) on neutrophils and macrophages that allows these cells to adhere to and enter the gastrointestinal tract to trigger acute, severe inflammation (*possible use in C. diff*)

2nd clinical correlation: SEGS (neutrophils)...flow along the margins (margination), stick to the walls of the blood vessels (pavementing), leave the blood vessels (migration), engulf the pathogen, and release their granules (degranulation)—good in small amounts—not good when attacking our own tissues



To the rescue: Corticosteroids (Prednisone, dexamethasone) are potent anti-inflammatory drugs

- Steroids inhibit migration, engulfment and degranulation of the neutrophil; hence, its potent anti-inflammatory properties
- Why do we use Prednisone with autoimmune disease? For two reasons:
 - 1) To inhibit the damage caused by one’s own neutrophils attacking various tissues--24 hour relief; can cause a profound decrease in active inflammation within 4.5 hours—EX: bridging therapy in RA patients; used with “flare-ups” of lupus nephritis
 - 2) steroids are also immunosuppressants and suppress the immune response

Prednisone and side effects

- High-dose prednisone causes the breakdown of stored glycogen (glycogenolysis)—increases blood sugar and can contribute to secondary diabetes;
- One way to prevent this is to co-administer glucophage/metformin with Prednisone; prednisone triggers glycogenolysis in the liver, metformin inhibits glycogenolysis—metformin WINS ☺
- Blood sugars won’t go up

THE MACROPHAGE: Cells of chronic inflammation; also process and present antigens to the specific immune cells

- BRIDGE between inflammation and immunity
- The cell of chronic inflammation--these cells respond much slower than the neutrophil (2-4 days vs. 5-10 minutes for the neutrophil, the cell of acute inflammation)
- MACRO—BIG; PHAGE—EATER (PIG)It engulfs the pathogen; chews it up and processes it and presents it to the helper T cell (T4 cell) – one of the “effector cells of the immune system”

The macrophage releases “cytokines” as it engulfs and presents

- Interleukins— “inter”= between and “leukins”—white blood cells (leukocytes); there are 36 of them...SERIOUSLY?? Abbreviated IL-1, IL-2, IL-6, IL-17, IL-23....get it? Aren't you happy we won't be talking about ALL of them? Many of these interleukins are INFLAMMATORY
- **WHAT ELSE do macrophages release?**
- Tumor necrosis factor alpha (TNF- α)—a potent inflammatory mediator
- Interferons (IFN)—3 types—alpha (anti-viral), beta (immunosuppressing), and gamma interferon (immune-enhancing)
- Janus kinases—enzymes contributing to cellular growth as well as inflammation

Clinical/pharmacological correlation

- Tumor necrosis factor alpha (TNF- α)—a potent inflammatory mediator—can be OVERexpressed in autoimmune diseases such as Rheumatoid Arthritis, Crohn's disease, Ulcerative colitis, psoriatic arthritis
- Monoclonal antibodies that block TNF- α – infliximab (Remicade), adalimumab (Humira), certolizumab – pegol (Cimzia)
- **IMPORTANT:** TNF-alpha is an essential inflammatory mediator that keeps LTBI (Latent TB infection) in check – TB testing is imperative prior to initiating any of the drugs that block TNF-alpha; HBV testing as well (can reactivate with these drugs)
- Watch out for disseminated fungal infections while ON these drugs! And, an increased risk of herpes zoster and lymphoma

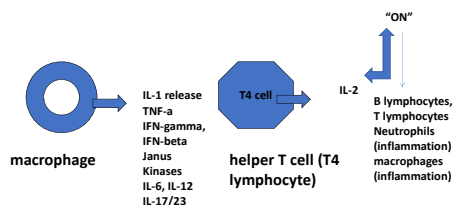
Clinical/pharmacological correlation

- Interferons (IFN)—3 types—alpha (anti-viral), beta (immunosuppressing), and gamma interferon (immune-enhancing)
- Interferon -alpha for hepatitis (not any more)
- Interferon beta (immunosuppressing)—Avonex (interferon beta 1a), Rebif (interferon beta 1a), Betaseron (interferon beta 1b), Plegridy (peginterferon beta-1a) for MS patients
- Janus kinases—enzymes contributing to cellular growth as well as inflammation – tofacitanib (Xeljanz) for rheumatoid arthritis (tyrosine kinase inhibitor)

Cells of the immune system—B lymphocytes and T lymphocytes

- B lymphocytes, when stimulated—turn into plasma cells—mean, green antibody-producing machines – plasma cells produce antibodies to foreign proteins (unfortunately that can also mean “self” in autoimmune diseases)
- T lymphocytes—killer Ts, memory Ts, helper Ts, regulatory cells Ts (T regs); T lymphocytes can also target “self”

Let’s put it all together—activating the immune system Gulp, chew, process, spit, kick...macrophages



Clinical correlation:

- Interferon-gamma release assay (IGRA)-- measures the production of interferon-gamma by the macrophages (chronic inflammatory response) in response to *M. tuberculosis* antigen stimulation. Specificity is superior; eliminates cross-reactivity with the BCG vaccine strain that is still routinely used in many countries, including Canada in some high TB–burden northern communities

Pharmacology correlation: More on drugs and how they influence the immune response

- Prednisone (corticosteroids) also inhibit IL-1 (interleukin-1) release—immunosuppressive (Lupus, MG, AIHA, ITP, RA as bridging therapy to the longer-acting DMARDs*)
- Methotrexate--blocks the binding of interleukin-1 to the interleukin 1 receptor on target cells; inhibits T cell activation
- Hydroxychlorine (Plaquenil) (Lupus)--increases the pH of the macrophage cytoplasmic compartment and decreases the immune/inflammatory response
- *DMARDs—disease modifying anti-rheumatic drugs such as Methotrexate

Pharmacology correlation: More on drugs and how they influence this immune response

- Cyclosporine inhibits IL-2—used to reduce tissue transplant rejection
- Leflunomide (Arava)—inhibits T and B lymphocyte proliferation
- Teriflunomide (Aubagio) 2nd generation leflunomide – same MOA
- Abatacept (Orencia)– “selective co-stimulation” modulator works by inhibiting T cell activation (Genovese MC et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005 Sep 15; 353: 1114-23
- Etanercept (Enbrel) binds to and inactivates excess TNF-a molecules— potent anti-inflammatory drug (psoriatic arthritis, Crohn disease, RA)
- (TB and HBV test before starting tofacitinib and etanercept)*

What other drugs influence the immune response?

- Mycophenolate mofetil (Cellcept)—mycophenolate sodium as **Myfortic**.—inhibits an enzyme involved in T and B cell activation
- Azathioprine (Muran)—inhibits T cell activation

IL-17/23 interleukins are crucial in the pathogenesis of psoriasis

- IL-17 and IL-23 are cytokines that control cell division and activate inflammation.
- In someone with psoriasis, the signals in the normal healing process of skin due to minor trauma are faulty. The tissue overreacts to an injury in the skin, or the immune system will mobilize for an unknown reason. People with psoriasis lesions, in particular, have **30 times more of the inflammatory interleukin, IL-17**, than people without lesions, Bagel et al. August 2012 *Practical Dermatology*.
- Studies have clearly demonstrated that either blocking or reducing IL-17 can help clear psoriasis.

IL-17/23 blocking monoclonal antibodies

- Ustekinumab (Stelara) to IL-12 and IL-23--psoriasis and psoriatic arthritis(now used for Crohn's disease as well)
- Secukinumab/Cosyntex – 81% of patients with a 75% improvement in symptoms
- Ixekizumab (Taltz) (IL-17 target)
- Guselkumab (Tremfya) (IL-23 target)
- Brodalumab (Siliq) (IL-23)

Let's put it all together with inflammatory bowel disease (Crohn's disease, Ulcerative colitis)

- Cause? Could IBD be caused by a imbalance in our own intestinal microflora that triggers an autoimmune disease? Previous norovirus infection in Crohn's disease
- Norovirus triggers inflammation; may "cross-react" with small intestine (or anywhere in GI tract)
- Autoimmune response with significant inflammation secondary to tumor necrosis factor-alpha, and other inflammatory interleukins
- "skip lesions"

Ulcerative colitis—inflammatory bowel disease

- Inflammation limited to the colon and rectum and affects only the mucosa and submucosa; extends in a continuous fashion proximally from the rectum

Treat to target

- Goals for UC—resolution of rectal bleeding and diarrhea and endoscopic remission
- Goals for CD—resolution of abdominal pain and diarrhea and resolution of ulceration at ileocolonoscopy
- Aggressive early intervention (within 18 months of diagnosis) is associated with better outcomes (especially Crohn’s disease)

Treatment of inflammatory bowel disease

- Oral corticosteroids (Prednisone)(Budesonide) for both Crohn’s and UC for the acute inflammation
- Then taper and discontinue
- Rectal corticosteroids for rectal and distal ulcerative colitis
- Enemas can reach the splenic flexure, while foam coats only the last 15-20 cm of the colon
- Budesonide (Entocort EC) enemas 2 gm/day are equally effective

Immunomodulatory agents

- Cyclosporine (Sandimmune) -- IV for severe steroid-resistant UC who are candidates for procto-colectomy
- Methotrexate inhibits T cell activation; inhibition of enzyme activity leading to the deactivation of enzyme activity relevant to immune system function
- Monoclonal antibodies -- moderate to severe UC and CD not responsive to conventional therapies; infliximab (Remicade) reduces the risk of colectomies in UC and decreases hospitalization rates
- Colectomy in UC patients: Placebo -- 17%; 5 mg/kg of infliximab --12%; 10 mg/kg of infliximab -- 8%; 20 vs. 40 hospitalizations) (Sandborn)
- Treatment Guidelines from The Medical Letter, vol. 7(85): September 2013

Medical treatment UC

- Aminosaliclates—the active moiety of all the aminosaliclates used to treat IBD is 5-aminosalicylate (5-ASA), aka mesalamine
- Oral mesalamine is absorbed in the small intestine and doesn't reach the colon; Pentasa releases mesalamine gradually throughout the GI tract
- Sulfasalazine (Asulfidine), balsalazide (Colazal), olsalazine (Dipentum) are prodrugs released in the colon following bacterial cleavage of the prodrug bond
- Lialda (mesalamine) and Apriso (mesalamine) both delay the release of the drug until it reaches the distal ileum and colon
- Rectal mesalamine (Rowasa as an enema and Canasa as a rectal suppository); balsalazide (Colazal)

TNF- α inhibitors—moderate to severe CD and UC

- Drugs that target TNF-alpha include
 - infliximab (Remicade) – most experience
 - adalimumab (Humira) – for patients intolerant to infliximab or lack of response to infliximab;
 - certolizumab pegol (Cimzia) (as above); golimumab (Simponi)
- TB, HBV testing BEFORE using these drugs!!
- Drug monitoring (drug levels) and antidrug antibodies can be drawn for non-responders

The Medical Letter (December 23, 2013); 55(1432)

Antibiotics for patients with Crohn's disease?

- Antibiotics may be particularly helpful for Crohn's disease due to possible alterations in the balance of enteric bacteria as a cause; antibiotics are also used to treat the complications of Crohn's-- colitis and ileocolitis, microperforations, fistulas, pouchitis
- Metronidazole (Flagyl)
- Ciprofloxacin (Cipro)
- Rifaximin (Xifaxin)
- VITAMIN D for Crohn's disease?

And that's just a start for autoimmune disease!
Thanks...

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